Synthesis of Novel 3- and 5-Substituted Indole-2-Carboxamides

Larry D. Bratton*, Bruce D. Roth, Bharat K. Trivedi and Paul C. Unangst

Department of Chemistry, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, MI 48105

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The preparation of several novel 3,5-substituted-indole-2-carboxamides is described. A 5-nitro-indole-2-carboxylate was elaborated to the 3-benzhydryl ester, *N*-substituted ester, and carboxylic acid intermediates, followed by conversion to the amide and then reduction of the 5-nitro group to the amine. Indole-2-carboxamides with 3-benzyl and 3-phenyl substituents were prepared in four steps from either a 3-bromo indole ester using the Suzuki reaction or from a 3-keto substituted indole ester. *N*-Alkylation of ethyl indole-2-carboxylate, followed by amidation and catalytic addition of 9-hydroxyxanthene gave a 3-xanthyl-indole-2-carboxamide analog and a spiropyrrolo indole as a side product.

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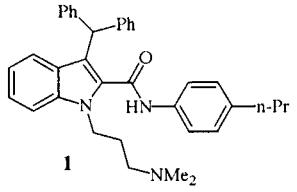
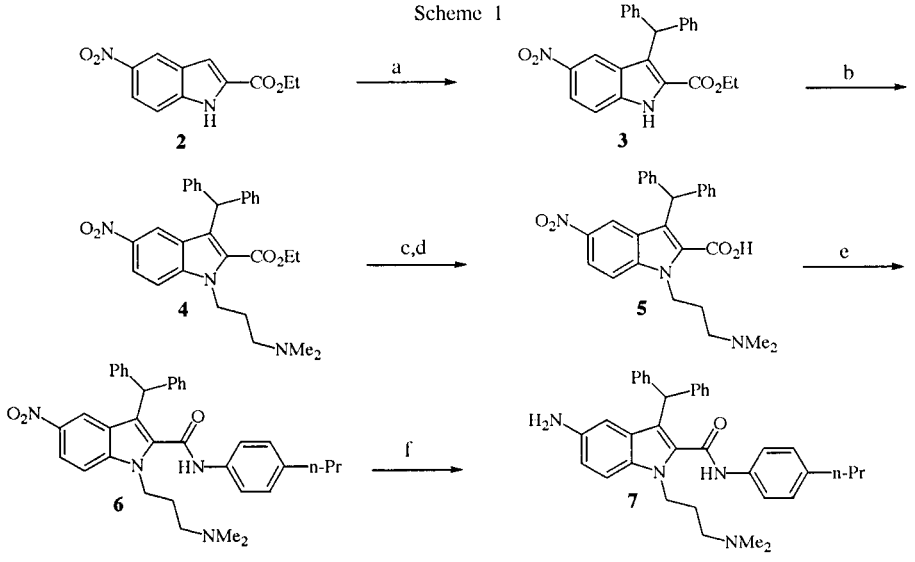
We have maintained a continuing interest in the chemistry and potential pharmacological activity of 3-substituted-indole-2-carboxamides [1-3]. As part of a screening program to identify new compounds with pharmacological activity, we became interested in the 3-benzhydryl-indole **1**. Compound **1** and related derivatives were originally prepared [4] as therapeutic agents for the treatment of osteoporosis. In this paper, we describe the preparation of 5-nitro and 5-amino analogs of **1**, as well as examples in which the 3-benzhydryl substituent has been replaced by phenyl, benzyl, and 9-xanthyl functionalities.



1

Preparation of the target 5-aminoindole-2-carboxamide began with the commercially available nitro ester **2** (Scheme 1). Introduction of the benzhydryl moiety [5] was achieved by electrophilic aromatic substitution on the 3-position of **2** using methanesulfonic acid as the catalyst. This reaction gave exclusively the 3-substituted analog in 89% yield. Treatment of the benzhydryl ester **3** with excess sodium hydride in *N*,*N*-dimethylformamide, followed by alkylation with 3-dimethylaminopropyl chloride hydrochloride yielded the *N*-substituted indole ester **4** (83% yield). Saponification of **4** with sodium hydroxide gave the crude carboxylic acid derivative **5**. Initial attempts to synthesize the nitro carboxamide **6** from the acid chloride of **5** under modified Schotten-Baumann reaction conditions were unsuccessful. Therefore, **6** was prepared by treatment of the carboxylic acid **5** with the coupling agent bis (2-oxo-3-oxazolidinyl) phosphinic chloride (BOP-Cl) [6] and 4-propylaniline under basic conditions. Formation of the final target amino carbox-

Scheme 1



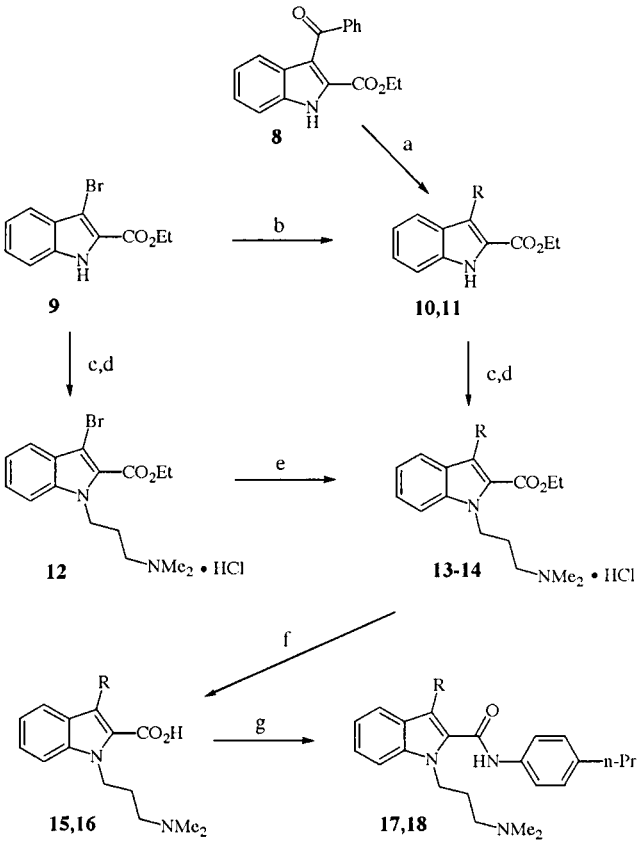
2 **3** **4** **5** **6** **7**

a) Benzhydrol, $MeSO_3H$; b) NaH, $Me_2N(CH_2)_3Cl \cdot HCl$; c) NaOH; d) HCl; e) 4-Propylaniline, BOP-Cl, *N*,*N*-diisopropylethylamine; f) Raney Nickel, H_2.

amide **7** was achieved in 78% yield by catalytic hydrogenolysis of the nitro group of **6**.

Synthesis of the target 3-benzyl and 3-phenyl substituted indole-2-carboxamide analogs employed the indole esters **10** [7] and **11** [8] as key intermediates (Scheme 2). These esters were previously prepared in the literature by the Fischer indole reaction. We found it more convenient to prepare **10** (84% yield) by the reaction of the bromo derivative **9** [9] with phenyl boronic acid under Suzuki reaction conditions. Intermediate **11** was obtained in 75% yield by the reduction of ketone **8** [10] with triethylsilane and trifluoroacetic acid. Alkylation with 3-dimethylaminopropyl chloride gave *N*-substituted indoles **12-14**. Alternatively, preparation of **13** was also possible by a modified Suzuki reaction on the free base of **12**. Saponification of esters **13** and **14** gave the corresponding carboxylic acids **15** and **16**, and activation of the acids with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), followed by amidation with 4-propylaniline yielded the target 3-aryl substituted indole-2-carboxamides **17** and **18**.

Scheme 2

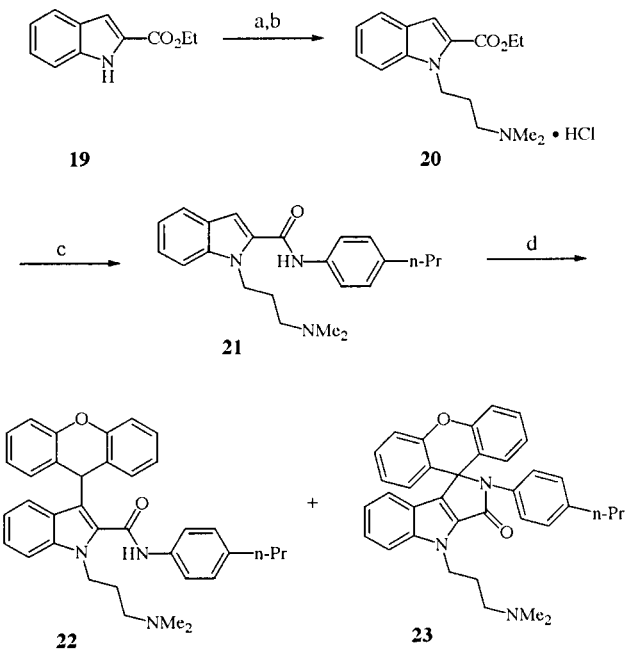


10,13,15,17 R = Ph
11,14,16,18 R = $PhCH_2$

a) Et_3SiH, TFA; b) $PhB(OH)_2$, $Pd(PPh_3)_4$; c) $Me_2N(CH_2)_3Cl \cdot HCl$, NaH; d) HCl; e) $PhB(OH)_2$, $Pd(PPh_3)_4$; f) NaOH; g) 4-Propylaniline, 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride.

The final 3-xanthylindole-2-carboxamide analog was prepared in three steps (Scheme 3) from commercially available ester **19** using a slightly different synthetic approach. Alkylation of **19** provided the ester derivative **20**. Compound **20** reacted with 4-propylaniline and lithium diisopropylamide (LDA) to afford carboxamide **21** in 93% yield. Finally, addition of 9-hydroxyxanthene to **21** using boron trifluoride etherate as catalyst gave the desired adduct **22** as well as the cyclized byproduct **23**. The structure of **23** was determined by an attached proton test (APT) and a long range two-dimensional ^{13}C and ^{1}H nuclear magnetic resonance correlation experiment (FLOCK).

Scheme 3



a) $Me_2N(CH_2)_3Cl \cdot HCl$, NaH; b) HCl; c) 4-Propylaniline, n-BuLi, $(i\text{-}Pr)_2NH$; d) 9-Hydroxyxanthene, $BF_3 \cdot Et_2O$.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary or Electrothermal apparatus and are uncorrected. Elemental Analysis was performed by Quantitative Technologies, Inc. (Whitehouse, N. J.). The ^{1}H NMR spectra were recorded on a Varian Unity 400 Nuclear Magnetic Resonance spectrometer with chemical shifts reported in ppm relative to internal tetramethylsilane. Mass spectra were recorded on a Micromass Platform LC mass spectrometer operating at atmospheric pressure. Infrared spectra were recorded as potassium bromide disks on a Mattson NU 30,000 FT IR or a Biorad FTS 45 IR spectrometer. Reactions were run under a nitrogen atmosphere unless otherwise stated, and solutions were concentrated at aspirator

vacuum on a rotary evaporator. Flash chromatography was performed with EM Science silica gel 60, 230-400 mesh ASTM.

Ethyl 3-benzhydryl-5-nitro-1*H*-indole-2-carboxylate (**3**).

To a solution of **2** (1.0 g, 4.3 mmoles) in 40 ml of a 1:1 mixture of dichloromethane and chloroform was added benzhydrol (0.90 g, 4.7 mmoles), followed by 0.83 ml (12.8 mmoles) of methanesulfonic acid. The solution was stirred at room temperature for 18 hours and 200 ml of saturated aqueous sodium bicarbonate was added to the reaction mixture. After stirring for 15 minutes, the organic layer was separated, dried over anhydrous sodium sulfate, filtered, and evaporated. Purification by flash chromatography (30% ethyl acetate/hexane) afforded 1.5 g (89%) of **3**. A sample recrystallized from ethyl acetate/hexane had mp 226-228°; ir: 3305, 1677, 1331, 1260, 1245 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.25 (t, J = 6.8 Hz, 3H), 4.29 (q, J = 7.5 Hz, 2H), 6.59 (s, 1H), 7.07 (d, J = 7.3 Hz, 4H), 7.15-7.30 (m, 6H), 7.55 (d, J = 9.1 Hz, 1H), 7.62 (s, 1H), 7.99 (d, J = 9.2 Hz, 1H), 12.49 (s, 1H); ms: *m/z* 401 $(M+1)^+$.

Anal. Calcd. for $C_{24}H_{20}N_2O_4$: C, 71.99; H, 5.03; N, 7.00. Found: C, 71.97; H, 4.88; N, 6.92.

Ethyl 3-benzhydryl-1-(3-dimethylamino-propyl)-5-nitro-1*H*-indole-2-carboxylate (**4**).

To a suspension of sodium hydride (0.18 g, 4.9 mmoles) in 12 ml of anhydrous *N,N*-dimethylformamide was slowly added the ester derivative **3** (0.94 g, 2.3 mmoles). The mixture was stirred for 30 minutes and then treated with 3-dimethylaminopropyl chloride hydrochloride (0.39 g, 2.5 mmoles). The reaction mixture was heated to 80° and stirred for 3 hours. After cooling to room temperature, the mixture was treated with 10 ml of saturated ammonium chloride. The solvent was evaporated, and the residue was extracted with three 100 ml portions of chloroform. The filtered extracts were washed with three 100 ml portions of saturated sodium bicarbonate, dried over anhydrous sodium sulfate, filtered, and evaporated. Purification by flash chromatography (70% ethyl acetate/methanol) yielded 0.88 g (83%) of **4**, mp 128-131°; ir: 1715, 1516, 1335, 1313, 1202 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.20 (t, J = 7.2 Hz, 3H), 1.71-1.84 (m, 2H), 1.97 (s, 6H), 2.01 (t, J = 6.6 Hz, 2H), 4.21 (q, J = 6.9 Hz, 2H), 4.52 (t, J = 7.0 Hz, 2H), 6.43 (s, 1H), 7.05 (d, J = 7.6 Hz, 4H), 7.19 (t, J = 6.6 Hz, 2H), 7.26 (t, J = 7.5 Hz, 4H), 7.65 (s, 1H), 7.77 (d, J = 9.7 Hz, 1H), 8.02 (d, J = 9.3 Hz, 1H); ms: *m/z* 486 $(M+1)^+$.

Anal. Calcd. for $C_{29}H_{31}N_3O_4$: C, 71.73; H, 6.43; N, 8.65. Found: C, 71.48; H, 6.38; N, 8.53.

3-Benzhydryl-1-(3-dimethylamino-propyl)-5-nitro-1*H*-indole-2-(4-propyl-phenyl)-amide (**6**).

A mixture of 17.8 ml of 2*N* aqueous sodium hydroxide solution, 50 ml of ethanol, and **4** (5.8 g, 12.7 mmoles) was heated to reflux and stirred for 4 hours. After cooling to room temperature, the solvent was evaporated, and the residue was treated with 50 ml of water and acidified with 1*N* hydrochloric acid to pH = 6. The solid was filtered and dried to yield 4.9 g (93%) of the crude acid intermediate **5**, mp 235° (dec.); ir: 3429, 3407, 1595, 1515, 1330 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.12-2.24 (m, 2H), 2.50 (s, 6H), 2.73 (t, J = 5.9 Hz, 2H), 4.57 (t, J = 6.6 Hz, 2H), 6.74 (s, 2H), 7.04-7.16 (m, 6H), 7.21 (t, J = 7.3 Hz, 4H), 7.66 (d, J = 9.2 Hz, 1H), 7.75 (s, 1H), 7.90 (d, J = 8.9 Hz, 1H), 13.39 (bs, 1H); ms: *m/z* 458 $(M+1)^+$.

To a solution of **5** (1.5 g, 3.3 mmoles) in 40 ml of anhydrous dichloromethane and 1.7 ml (9.8 mmoles) of *N,N*-diisopropylethylamine was added bis (2-oxo-3-oxazolidinyl) phosphinic chloride (0.90 g, 3.6 mmoles). The solution was stirred at room temperature for 1.5 hours and then treated with 4-propylaniline (0.50 g, 3.6 mmoles). The solution was stirred for 18 hours, and the solvent was evaporated. Purification by flash chromatography (70% ethyl acetate/methanol) yielded 0.97 g (51%) of **6**. A sample recrystallized from acetone had mp 179-180°; ir: 1661, 1539, 1517, 1335, 1314 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.83 (t, J = 7.2 Hz, 3H), 1.43-1.60 (m, 2H), 1.72-1.86 (m, 2H), 1.95 (s, 6H), 2.06 (t, J = 6.7 Hz, 2H), 2.40-2.51 (m, 2H), 4.30 (t, J = 7.08 Hz, 2H), 5.99 (s, 1H), 7.03-7.28 (m, 12H), 7.37 (d, J = 8.5 Hz, 2H), 7.76 (d, J = 9.2 Hz, 1H), 7.80 (d, J = 2.2 Hz, 1H), 8.01 (dd, J = 9.2, 2.2 Hz, 1H), 10.50 (s, 1H); ms: *m/z* 575 $(M+H)^+$.

Anal. Calcd. for $C_{36}H_{38}N_4O_3$: C, 75.24; H, 6.66; N, 9.75. Found: C, 75.01; H, 6.63; N, 9.73.

5-Amino-3-benzhydryl-1-(3-dimethylamino-propyl)-1*H*-indole-2-(4-propyl-phenyl)-amide (**7**).

A mixture of **6** (0.72 g, 1.3 mmoles) and Raney nickel (0.30 g) in 25 ml of tetrahydrofuran and 25 ml of methanol was shaken under hydrogen at 50 psi and room temperature for 18 hours. The mixture was filtered through Celite filter aid and the filtrate was evaporated. Purification by flash chromatography (70% ethyl acetate/methanol), followed by trituration in ethyl acetate afforded 0.53 g (78%) of **7**, mp 143-145°; ir: 3380, 1675, 1661, 1541, 1516 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.77-0.89 (t, J = 7.4 Hz, 3H), 1.42-1.60 (m, 2H), 1.62-1.79 (m, 2H), 1.94 (s, 6H), 1.99 (t, J = 6.9 Hz, 2H), 2.40-2.52 (m, 2H), 4.13 (t, J = 6.8 Hz, 2H), 4.44 (bs, 2H), 5.81 (s, 1H), 6.28 (s, 1H), 6.53 (dd, J = 8.6, 2.1 Hz, 1H), 7.02-7.25 (m, 13H), 7.47 (d, J = 8.3 Hz, 2H), 10.31 (s, 1H); ms: *m/z* 545 $(M+1)^+$.

Anal. Calcd. for $C_{36}H_{40}N_4O$: C, 79.38; H, 7.40; N, 10.28. Found: C, 78.98; H, 7.44; N, 10.16.

Ethyl 3-phenyl-1*H*-indole-2-carboxylate (**10**).

To a solution of **9** (11.2 g, 41.8 mmoles) and phenyl boronic acid (7.4 g, 60.7 mmoles) in 500 ml of a 1:1 mixture of toluene and ethanol was added 105 ml of 1.0 *M* aqueous sodium carbonate (105 mmoles), followed by lithium chloride (5.0 g, 118 mmoles) and tetrakis(triphenylphosphine)palladium (2.3 g, 2.1 mmoles). The mixture was heated to reflux and stirred for 4 hours. After cooling to room temperature, 400 ml of ethyl acetate was added, and the reaction mixture was filtered through Celite filter aid. The filtrate was washed with two 500 ml portions of 5% aqueous sodium carbonate and 500 ml of brine. The organic layer was dried (anhydrous sodium sulfate) and evaporated. Purification by flash chromatography (15% ethyl acetate/hexane) yielded 9.3 g (84%) of **10**. A sample recrystallized from hexane had mp 137-139° (lit [9] mp 137-138°); ir: 3321, 1675, 1383, 1334, 1255 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.12 (t, J = 7.2 Hz, 3H), 4.16 (q, J = 7.1 Hz, 2H), 7.04 (t, J = 7.6 Hz, 1H), 7.25 (t, J = 7.6 Hz, 1H), 7.31 (t, J = 7.1 Hz, 1H), 7.36-7.48 (m, 6H), 11.87 (s, 1H); ms: *m/z* 266 $(M+1)^+$.

Anal. Calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.05; H, 5.72; N, 5.19.

Ethyl 3-benzyl-1*H*-indole-2-carboxylate (**11**).

To a solution of **8** (6.2 g, 21.1 mmoles) in 30 ml of trifluoroacetic acid was added 12.9 ml (80.8 mmoles) of triethylsilane. The reaction mixture was stirred at room temperature for 16 hours, after which time a precipitate formed. The mixture was filtered, and the solid material was washed twice with hexane to afford 4.4 g (75%) of **11**. A sample recrystallized from ethyl acetate/hexane had mp 151-153° (lit [10] mp 145.5-146.5°); ir: 3316, 1680, 1334, 1262, 1227 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.33 (t, J = 7.1 Hz, 3H), 4.35 (q, J = 7.1 Hz, 2H), 4.44 (s, 2H), 7.03 (t, J = 7.6 Hz, 1H), 7.12 (t, J = 7.1 Hz, 1H), 7.17-7.32 (m, 5H), 7.43 (d, J = 8.3 Hz, 1H), 7.64 (d, J = 8.2 Hz, 1H), 11.63 (s, 1H); ms: *m/z* 278 $(M-1)^-$.

Anal. Calcd. for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.46; H, 6.03; N, 4.92.

Ethyl 3-bromo-1-(3-dimethylamino-propyl)-1*H*-indole-2-carboxylate hydrochloride (**12**).

The free base of **12** was prepared from **9** (9.2 g, 34.3 mmoles) as described for the preparation of **4**. Purification by flash chromatography (3% triethylamine in ethyl acetate) gave 7.8 g (64%) of the free base as an oil; ^1H NMR (deuteriochloroform): δ 1.43 (t, J = 7.1 Hz, 3H), 1.86-1.94 (m, 2H), 2.17 (s, 6H), 2.21 (t, J = 7.0 Hz, 2H), 4.41 (q, J = 7.1 Hz, 2H), 4.55 (t, J = 7.2 Hz, 2H), 7.18 (t, J = 7.4 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.42 (d, J = 8.6 Hz, 1H), 7.63 (d, J = 8.1 Hz, 1H).

The above free base (0.50 g) was dissolved in 20 ml of diethyl ether, cooled in an ice bath, and treated with 10 ml of a saturated solution of anhydrous hydrochloric acid in diethyl ether. The mixture was stirred for 1 hour, and the precipitated solid was filtered and rinsed with diethyl ether to afford **12**. A sample recrystallized from *t*-butyl methyl ether/2-propanol had mp 188-190°; ir: 3431, 1702, 1499, 1260, 1216 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.34 (t, J = 7.1 Hz, 3H), 2.02-2.14 (m, 2H), 2.66 (s, 6H), 3.05 (t, J = 8.0 Hz, 2H), 4.36 (q, J = 7.1 Hz, 2H), 4.57 (t, J = 7.4 Hz, 2H), 7.23 (t, J = 7.5 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 8.5 Hz, 1H), 10.34 (bs, 1H); ms: *m/z* 353 $(M+1-HCl)^+$.

Anal. Calcd. for $C_{16}H_{21}BrN_2O_2$ x HCl: C, 49.31; H, 5.69; N, 7.19. Found: C, 49.16; H, 5.62; N, 7.01.

Ethyl 1-(3-dimethylamino-propyl)-3-phenyl-1*H*-indole-2-carboxylate hydrochloride (**13**).

Method A.

The free base of **13** was prepared from **10** (1.4 g, 5.3 mmoles) by the procedure described for the preparation of **4** to yield 0.90 g (50%) of the free base as an oil; ^1H NMR (deuteriochloroform): δ 0.96 (t, J = 7.1 Hz, 3H), 1.90-2.01 (m, 2H), 2.17 (s, 6H), 2.26 (t, J = 7.0 Hz, 2H), 4.09 (q, J = 7.2 Hz, 2H), 4.54 (t, J = 7.4 Hz, 2H), 7.06 (t, J = 7.6 Hz, 1H), 7.23-7.39 (m, 6H), 7.43 (d, J = 8.4 Hz, 1H), 7.48 (d, J = 8.1 Hz, 1H).

The hydrochloride salt **13** was prepared from the above free base (0.40 g) by the procedure described for the preparation of **12**. A sample of **13** recrystallized from *t*-butyl methyl ether/2-propanol had mp 154-156°; ir: 1694, 1260, 1247, 1190, 1124 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.94 (t, J = 7.1 Hz, 3H), 2.06-2.20 (m, 2H), 2.69 (s, 6H), 3.11 (t, J = 7.9 Hz, 2H), 4.09 (q, J = 7.0 Hz, 2H), 4.54 (t, J = 7.4 Hz, 2H), 7.11 (t, J = 7.5 Hz, 1H), 7.29-7.47 (m, 7H), 7.70 (d, J = 8.4 Hz, 1H), 10.35 (bs, 1H); ms: *m/z* 351 $(M+1-HCl)^+$.

Anal. Calcd. for $C_{22}H_{26}N_2O_2$ x HCl: C, 68.29; H, 7.03; N, 7.24. Found: C, 68.68; H, 7.08; N, 7.19.

Method B.

A mixture of the free base of **12** (0.55 g, 1.56 mmoles) and tetrakis(triphenylphosphine)palladium (0.06 g, 0.05 mmoles) were combined in 15 ml of ethylene glycol dimethyl ether. The mixture was stirred for 10 minutes and then phenyl boronic acid (0.21 g, 1.7 mmoles) was added, followed by a solution of aqueous sodium bicarbonate (0.40 g, 4.8 mmoles) in 7 ml of water. The mixture was heated to reflux and stirred for 4 hours. After cooling to room temperature, the reaction mixture was diluted with 75 ml of ethyl acetate and then filtered through Celite filter aid. The filtrate was evaporated to an oil, which was partitioned between 75 ml of ethyl acetate and 150 ml of brine. The aqueous layer was extracted with three 75 ml portions of ethyl acetate. The combined organic extracts were washed with two 200 ml portions of 5% aqueous sodium bicarbonate, 200 ml of brine, then dried, and evaporated. Purification by flash chromatography (3% triethylamine in ethyl acetate) gave 0.26 g (47%) of the free base of **13** as an oil, identical with the product prepared from **10**.

Ethyl 3-benzyl-1-(3-dimethylamino-propyl)-1*H*-indole-2-carboxylate hydrochloride (**14**).

The free base of **14** was prepared from **11** (4.4 g, 15.8 mmoles) by the procedure described for the preparation of **4** to yield 2.2 g (39%) of the free base as an oil; ^1H NMR (deuteriochloroform): δ 1.23 (t, J = 7.1 Hz, 3H), 1.85-1.94 (m, 2H), 2.15 (s, 6H), 2.22 (t, J = 7.2 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 4.42 (s, 2H), 4.51 (t, J = 7.3 Hz, 2H), 7.00-7.18 (m, 6H), 7.26 (t, J = 7.7 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H); ms: *m/z* 365 $(M+1-HCl)^+$.

The hydrochloride salt **14** was prepared from the above free base by the procedure described for the preparation of **12**. A sample of **14** recrystallized from *t*-butyl methyl ether/2-propanol had mp 180-182°; ir: 1700, 1258, 1226, 1141, 1123 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.28 (t, J = 7.1 Hz, 3H), 2.06-2.19 (m, 2H), 2.73 (s, 6H), 3.12 (t, J = 7.9 Hz, 2H), 4.34 (q, J = 7.1 Hz, 2H), 4.44 (s, 2H), 4.56 (t, J = 7.4 Hz, 2H), 7.06-7.28 (m, 6H), 7.37 (t, J = 7.7 Hz, 1H), 7.67 (d, J = 8.6 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 10.34 (bs, 1H); ms: *m/z* 365 $(M+1-HCl)^+$.

Anal. Calcd. for $C_{23}H_{28}N_2O_2$ x HCl: C, 68.90; H, 7.29; N, 6.99. Found: C, 69.08; H, 7.36; N, 6.90.

3-Benzyl-1-(3-dimethylamino-propyl)-1*H*-indole-2-carboxylic acid (**16**).

Prepared from the free base of **14** (2.2 g, 6.0 mmoles) by the procedure described for the preparation of **5** to yield 1.8 g (90%) of **16**. A sample recrystallized from water/2-propanol had mp 207° (dec); ir: 3403, 1600, 1417, 1362, 1312 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.12-2.25 (m, 2H), 2.49 (s, 6H), 2.63 (t, J = 6.2

Hz, 2H), 4.38 (s, 2H), 4.56 (t, J = 6.7 Hz, 2H), 6.98 (t, J = 7.5 Hz, 1H), 7.06 (t, J = 7.1 Hz, 1H), 7.17 (t, J = 7.6 Hz, 3H), 7.30 (d, J = 7.5 Hz, 2H), 7.47 (t, J = 8.7 Hz, 2H); ms: *m/z* 337 $(M+1)^+$.

Anal. Calcd. for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.64; H, 7.23; N, 8.26.

1-(3-Dimethylaminopropyl)-3-phenyl-1*H*-indole-2-(4-propyl-phenyl)-amide (**17**).

The crude acid intermediate **15** was prepared from the free base of **13** (1.1 g, 3.1 mmoles) by the procedure described for the preparation of **5** to yield 0.93 g (93%) of **15**. A sample recrystallized from water/acetonitrile had mp 245° (dec); ir: 3430, 1591, 1412, 1354, 1316 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.18-2.31 (m, 2H), 2.53 (s, 6H), 2.71 (t, J = 6.1 Hz, 2H), 4.47 (t, J = 6.4 Hz, 2H), 7.09 (t, J = 7.25 Hz, 1H), 7.19-7.26 (m, 2H), 7.38 (t, J = 7.7 Hz, 2H), 7.50-7.57 (m, 3H), 7.59 (d, J = 8.1 Hz, 1H); ms: *m/z* 323 ($M+1)^+$.

To a solution of **15** (1.5 g, 4.7 mmoles) in 50 ml of anhydrous dichloromethane was added 0.80 ml (5.4 mmoles) of 4-propyl-aniline, followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodi-imide hydrochloride (1.8 g, 9.4 mmoles). The mixture was stirred at room temperature for 16 hours and then added to 350 ml of water. The aqueous mixture was extracted with four 100 ml portions of dichloromethane. The organic extracts were combined and washed with three 200 ml portions of 5% aqueous sodium bicarbonate, two 200 ml portions of brine, then dried, and evaporated. Purification by flash chromatography (3% triethylamine in ethyl acetate) gave 1.4 g (70%) of **17**. A sample recrystallized from hexane had mp 110-111°; ir: 1648, 1600, 1530, 1461, 1317 cm^{-1}; ^1H NMR (deuteriochloroform): δ 0.84 (t, J = 7.3 Hz, 3H), 1.45-1.58 (m, 2H), 1.96-2.08 (m, 2H), 2.18 (s, 6H), 2.30 (t, J = 6.6 Hz, 2H), 2.44 (t, J = 7.8 Hz, 2H), 4.61 (t, J = 7.2 Hz, 2H), 6.98 (s, 4H), 7.09 (t, J = 7.4 Hz, 1H), 7.24-7.56 (m, 9H); ms: *m/z* 440 $(M+1)^+$.

Anal. Calcd. for $C_{29}H_{33}N_3O$: C, 79.24; H, 7.57; N, 9.56. Found: C, 79.51; H, 7.56; N, 9.59.

3-Benzyl-1-(3-dimethylamino-propyl)-1*H*-indole-2-(4-propyl-phenyl)-amide (**18**).

Prepared from **16** (1.3 g, 3.9 mmoles) by the procedure described for the preparation of **17** to yield 1.4 g (78%) of **18**. A sample recrystallized from hexane had mp 125-127°; ir: 3261, 1640, 1602, 1557, 1540 cm^{-1}; ^1H NMR (deuteriochloroform): δ 0.85 (t, J = 7.3 Hz, 3H), 1.48-1.60 (m, 2H), 1.93-2.05 (m, 2H), 2.11 (s, 6H), 2.20 (t, J = 6.9 Hz, 2H), 2.47 (t, J = 7.4 Hz, 2H), 4.34 (s, 2H), 4.46 (t, J = 7.1 Hz, 2H), 6.98-7.31 (m, 11H), 7.41 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 7.9 Hz, 1H), 8.01 (s, 1H); ms: *m/z* 454 $(M+1)^+$.

Anal. Calcd. for $C_{30}H_{35}N_3O$: C, 79.43; H, 7.78; N, 9.26. Found: C, 79.45; H, 7.80; N, 9.32.

Ethyl 1-(3-dimethylamino-propyl)-1*H*-indole-2-carboxylate hydrochloride (**20**).

The free base of **20** was prepared from **19** (9.5 g, 50.2 mmoles) by the procedure described for the preparation of **4** to yield 9.2 g (67%) of the free base as an oil; ^1H NMR (deuterio-chloroform): δ 1.34 (t, J = 7.2 Hz, 3H), 1.84-1.95 (m, 2H), 2.15 (s, 6H), 2.23 (t, J = 7.0 Hz, 2H), 4.30 (q, J = 7.0 Hz, 2H), 4.55 (t, J = 7.5 Hz, 2H), 7.07 (t, J = 7.5 Hz, 1H), 7.22-7.30 (m, 2H), 7.40 (d, J = 8.5 Hz, 1H), 7.60 (d, J = 7.0 Hz, 1H); ms: *m/z* 275 $(M+1)^+$.

The hydrochloride salt **20** was prepared from the above free base by the procedure described for the preparation of **12**. A sample of 20 recrystallized from *t*-butyl methyl ether/2-propanol had mp 164-166°; ir: 1710, 1519, 1474, 1250, 1213 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.35 (t, J = 7.1 Hz, 3H), 2.06-2.20 (m, 2H), 2.72 (s, 6H), 3.10 (t, J = 7.0 Hz, 2H), 4.34 (q, J = 7.0 Hz, 2H), 4.63 (t, J = 6.7 Hz, 2H), 7.16 (t, J = 7.5 Hz, 1H), 7.33 (s, 1H), 7.38 (t, J = 7.2 Hz, 1H), 7.71 (d, J = 7.3 Hz, 2H), 10.49 (bs, 1H); ms: *m/z* 275 $(M+1\text{-}HCl)^+$.

Anal. Calcd. for $C_{16}H_{22}N_2O_2$ x HCl: C, 61.83; H, 7.46; N, 9.01. Found: C, 61.96; H, 7.58; N, 8.97.

1-(3-Dimethylamino-propyl)-1*H*-indole-2-(4-propyl-phenyl)-amide (**21**).

A solution of 3.1 ml (24.0 mmoles) of diisopropylamine in 15 ml of tetrahydrofuran was cooled in an ice bath and treated with 16 ml of a solution of 1.6 *M* *n*-butyllithium (26.0 mmoles) in hexane. The reaction mixture was stirred for 15 minutes, and a solution of 1.6 ml (11.0 mmoles) of 4-propylaniline in 10 ml of tetrahydrofuran was added. After stirring for 15 minutes, the mixture was treated with a solution of the free base of **20** (2.1 g, 7.7 mmoles) in 15 ml of tetrahydrofuran. The cooling bath was removed, and the mixture was stirred for 90 minutes as it warmed to room temperature. The reaction mixture was added to 350 g of ice water, followed by the addition of ammonium chloride to pH = 9-10. The mixture was extracted with four 150 ml portions of ethyl acetate. The organic extracts were combined and washed with two 300 ml portions of 5% aqueous sodium bicarbonate, and 300 ml of brine, then dried, and evaporated. Purification by flash chromatography (4% triethylamine in ethyl acetate) gave 2.6 g (93%) of **21**. A sample recrystallized from hexane had mp 80-82°; ir: 1644, 1596, 1524, 1458, 1320 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.90 (t, J = 7.3 Hz, 3H), 1.52-1.65 (m, 2H), 1.78-1.90 (m, 2H), 2.09 (s, 6H), 2.16 (t, J = 7.0 Hz, 2H), 2.53 (t, J = 7.4 Hz, 2H), 4.57 (t, J = 7.1 Hz, 2H), 7.08-7.21 (m, 3H), 7.25-7.45 (m, 2H), 7.59 (d, J = 8.3 Hz, 1H), 7.64-7.72 (m, 3H), 10.27 (s, 1H); ms: *m/z* 364 $(M+1)^+$.

Anal. Calcd. for $C_{23}H_{29}N_3O$: C, 76.00; H, 8.04; N, 11.56. Found: C, 76.00; H, 7.84; N, 11.49.

1-(3-Dimethylamino-propyl)-3-(9*H*-xanthene-9-yl)-1*H*-indole-2-(4-propyl-phenyl)-amide (**22**) and 4-[3-(Dimethylamino)-propyl]-2-(4-propylphenyl)-spiro[pyrrolo[3,4-*b*]indole-1(2*H*)-9'-[9*H*]xanthen]-3(4*H*)-one (**23**).

To a solution of **21** (2.1 g, 5.7 mmoles) and 9-hydroxy-xanthene (1.2 g, 5.8 mmoles) in 20 ml of dichloromethane was added dropwise a solution of 2.3 ml (18.7 mmoles) of boron trifluoride etherate in 5 ml of dichloromethane. The reaction mixture was stirred at room temperature for 16 hours and then added to 300 ml of 5% aqueous sodium carbonate. The mixture was extracted with four 100 ml portions of dichloromethane. The organic extracts were combined, washed with two 300 ml portions of brine, then dried, and evaporated. Purification by flash chromatography (3% triethylamine in ethyl acetate)

yielded two products. The first product was identified as **22**. Recrystallization from ethyl acetate/hexane gave 0.55 g (18%) of **22**, mp 217-219°; ir: 1645, 1600, 1479, 1447, 1252 cm^{-1}; ^1H NMR (deuteriochloroform): δ 0.90 (t, J = 7.4 Hz, 3H), 1.52-1.65 (m, 2H), 2.13 (s, 10H), 2.52 (t, J = 7.4 Hz, 2H), 4.47 (t, J = 6.4 Hz, 2H), 6.02 (s, 1H), 6.86 (t, J = 7.4 Hz, 2H), 6.93-7.25 (m, 12H), 7.37 (t, J = 9.0 Hz, 2H), 9.81 (bs, 1H); ms: *m/z* 544 $(M+1)^+$.

Anal. Calcd. for $C_{36}H_{37}N_3O_2$: C, 79.53; H, 6.86; N, 7.73. Found: C, 79.59; H, 6.87; N, 7.66.

The second product (0.60 g, 19%) was identified as **23**. A sample recrystallized from hexane had mp 123-125°; ir: 1693, 1478, 1447, 1335, 1316 cm^{-1}; ^1H NMR (deuteriochloroform): δ 0.77 (t, J = 7.3 Hz, 3H), 1.37-1.51 (m, 2H), 2.07-2.24 (m, 8H), 2.31-2.39 (m, 4H), 4.55 (t, J = 7.2 Hz, 2H), 6.39 (d, J = 8.3 Hz, 2H), 6.79 (d, J = 8.3 Hz, 2H), 6.86-7.08 (m, 8H), 7.16-7.30 (m, 3H), 7.51 (d, J = 8.6 Hz, 1H); ms: *m/z* 542 $(M+1)^+$.

Anal. Calcd. for $C_{36}H_{35}N_3O_2$: C, 79.82; H, 6.51; N, 7.76. Found: C, 79.88; H, 6.53; N, 7.68.

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